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Appendix

I. Assisted function and peripheral stimulation

While electrical stimulation has been in clinical use for half a century, most of the early applications targeted the peripheral nervous system (or peripheral musculature directly) with the aim of replacing activity lost through injury or disease, and thereby restoring some of the lost function, the classic example being electrical stimulation of peroneal nerves to treat foot drop and improve walking after brain damage or SCI. Over time, the range and complexity of these peripheral interventions has increased, along with strong clinical evidence of their effectiveness (and limitations), as we discuss below.

Stimulation of the peripheral nervous system, using neuroprosthetic technology to activate either motor or sensory nerves, represents the most clinically accessible and well tested form of neuromodulation. Beyond the effects at the muscle and spinal levels, peripheral stimulation can also influence motor function by increasing cortical excitability. A detailed description of the history of these developments is beyond the scope of this review (for recent reviews see[1–3]). Here we summarise the current state of this field and the new issues it is addressing.

Functional electrical stimulation (FES), where small electrical pulses are applied to muscles or nerves to improve their function, has a long history and clear benefits[1] in comparison with, for instance, treadmill-based training. Indirect muscle activation can be achieved by stimulating sensory nerves to evoke a spinal reflex response, and regular use of this type of stimulation is associated with improved voluntary activation of the dorsiflexors, as well as more normal modulation of spinal reflex circuity[4]. With the advent of locomotor exoskeletons, emerging technology integrates FES muscle activation with mechanical robotic support[5]. These advances combine the advantage of structural support for the stance phase of walking, with stepping activity driven by stimulated muscle function. This combined approach increases the potential value of exoskeletons as rehabilitation tools, since they more actively engage the nervous system in the walking behaviour. Beyond walking function, there are recent efforts to use neuroprosthetic systems to improve hand and arm function in persons with SCI[6,7]. For this to be of value, there are at least two requirements that must be met. First, for muscles to be responsive to electrical stimulation, some of the spinal motor neurons innervating the muscle targeted by the stimulation must be intact. Second, for grasp to be functionally meaningful, it is necessary that the individual have sufficient volitional control of the more proximal muscles about the elbow and shoulder in order to transport the hand to the object. As with exoskeletons for walking function, there is emerging technology, recently applied in participants severely affected by stroke, that integrates exoskeletal assistance and multi-channel neuromuscular stimulation to support upper extremity reach-to-grasp movements during rehabilitation exercises[8]. This type of “closed loop

training environment" has clear applications for SCI, and further developments in closed loop systems which use decoded brain signals to activate peripheral muscles involved in reach and grasp[9,10] are discussed in section V below.

An alternative to the use of motor stimulation for its neuroprosthetic applications is the use of somatosensory stimulation to promote functional restoration by "priming"[11] cortical networks, and thereby increasing corticospinal excitability. The reduced rate and volume of corticospinal transmission associated with damage to the spinal cord is a primary contributor to impaired hand function after SCI[12]. The situation is further complicated by the maladaptive cortical reorganization that accompanies SCI. While maladaptive cortical reorganization has not been studied in persons with SCI to the extent it has been studied in persons with stroke, early evidence indicates that motor recovery after SCI is associated with cortical and spinal cord structural and functional reorganization[13]. There is a direct relationship between the level of functional connectivity and recovery of motor function in persons with SCI[14]. By increasing cortical excitability and promoting neuroplasticity through motor practice, it is possible to increase corticospinal transmission in persons with SCI. Among the more accessible approaches to increasing cortical excitability is the use of electrical stimulation to activate sensory pathways peripherally. In persons with tetraplegia who have sufficient corticospinal connectivity to achieve at least a minimal amount of voluntary thenar muscle activation, somatosensory stimulation combined with training is associated with improvements in grasp strength that exceed those of resistance training[15]. Based on the goal of increasing transmission through remaining descending pathways, an ongoing clinical trial (NCT02611375; see Table 1 and[16]) compares the relative value of different forms of stimulation (peripheral nerve stimulation versus transcranial direct current stimulation, with both groups compared to sham stimulation) for augmenting the effects of conventional fine motor training. Since both forms of stimulation are clinically accessible, and the study is designed as a pragmatic clinical trial performed in the real-world clinical setting the outcome is expected to have immediate applicability for clinical practice.

Achieving recovery and control of basic bodily functions, such as bladder and bowel continence, - and in persons with high cervical SCI, respiration -, is the highest shared priority of persons with paraplegia and tetraplegia and rated as important as recovering lower limb movement. The Finetech-Brindley sacral anterior root stimulation (SARS) device, an implantable neuroprosthesis providing electrical stimulation of the motor nerves innervating the bladder and bowel, has been in clinical use since the 1970's. This device marked a breakthrough in incontinence management, enabling effective bladder voiding as well as aiding bowel evacuation and penile erection. However, its wider use has been limited by the surgical procedures and their complications, requiring irreversible removal of sacral sensory nerve roots (posterior rhizotomy) to prevent spontaneous

voiding and sphincter dyssynergia. Another early approach involved electrical stimulation of sacral nerves, leading to the development of a sacral nerve neuromodulation device (Medtronic Interstim) which has also been shown to successfully improve bladder continence in SCI patients. The use of these implantable devices, and more recent iterations such as the extradural (SPARSI) and intrathecal (SPAIRS) sacral posterior and anterior root stimulator implants, which do not involve posterior rhizotomy, has recently been reviewed in detail[17]. Another area receiving considerable current attention is the possibility of treating pain associated with SCI, and indeed other pathologies, with electrical stimulation of the dorsal root ganglion (where the cell bodies of sensory neurons are located). There is a commercial development in this area and a number of ongoing clinical trials, although clinical trial data is not yet available and the mechanism of action is not known. It should be noted that clinical applications of these new developments will be dependent on maintaining the skillset of clinicians willing to perform these procedures and of course by convincing clinical studies on efficacy. In individuals with high cervical SCI, in whom diaphragmatic innervation is lost, diaphragmatic pacing stimulation (DPS) can be a viable alternative to breathing through mechanical ventilation. Depending on the approach, stimulating cuff electrodes are placed around the phrenic nerve (intrathoracic diaphragm pacing), or electrodes are placed in the diaphragm (intraperitoneal diaphragm pacing). Following participation in a diaphragm reconditioning program, over 70% of the individuals who have received these implants have been successfully weaned from mechanical ventilation[18].

Experimental advances in peripheral stimulation

Novel applications of peripheral neuromodulation are being explored in laboratory experiments, such as the recent application of a “closed-loop” neuroprosthetic interface which was designed to measure bladder fullness and prevent spontaneous voiding episodes without the need for dorsal rhizotomy in adult SCI rats[19]. Accurate recordings of bladder filling were achieved by implanting fine-diameter sensory nerve ''rootlets'' into insulated microchannels. This sensory feedback was utilised to adjust ventral root stimulation and modulate bladder emptying, which could be artificially stimulated on demand by electrically modulating nerve firing. The clinical translation of this approach is currently limited by challenges in maintaining stable sensory recordings long-term. Recently, embryonic stem cell-derived motor neurons implanted into denervated peripheral nerves in mice were shown to innervate skeletal muscle and optogenetic stimulation of the motor neurons led to active contractions in the muscle[20]. While far from clinical application, this highlights recent advances in stem cell biology which have potential future applications for ‘neuronal circuit building’ to reanimate denervated muscles.

II. Clinical application of neuromodulation approaches for spinal cord injury

Challenges

The main challenges to achieving widespread clinical application of neuromodulation for SCI outlined in Panel 1 relate to considerations regarding *accessibility, affordability, durability, feasibility* and *scalability* of the approaches, but also a deeper understanding of *mechanisms* will be crucial to realising the full potential of neuromodulation-based interventions, as will the appropriate *clinical trial design* to enable large-scale clinical trials, which are needed to fully evaluate treatment *efficacy*. An important consideration in relation to scalability (which also relates to accessibility, affordability and feasibility) is the relative cost and healthcare infrastructure required for the different interventions. Some neuromodulation interventions are inexpensive and use conventional, commercially available stimulation devices, enabling their widespread use, as is the case for peripheral stimulation devices. However, newer advances in peripheral stimulation techniques which integrate FES with exoskeletal assistance[5] will not be so easily scalable due to the high costs of dexterous robotic devices. tcSCS and tDCS both have the potential to be rapidly made available to persons with SCI on a large scale, offering cost efficient and safe approaches to treating SCI, although robust evidence for functional improvements with these methods is not yet available. Perhaps the most dramatic demonstrations of return of function have been with BMI approaches, which in several small-scale studies have enabled reach and grasp movements in persons with chronic tetraplegia[10,21]. However, these are the most challenging in terms of scalability since they require specialized equipment and expertise and complex and non-portable systems which, together with extremely high costs and a lack of large-scale commercial interest[22], precludes their widespread use. While this may improve as technology becomes more affordable and portable, this currently preludes large-scale clinical trials, the lack of which arguably remains the biggest challenge for widespread clinical application of neuromodulation for SCI. A further important challenge in relation to future clinical trial design is identifying the appropriate populations for enrollment, as discussed below.

A further consideration when implementing any neuromodulatory intervention is determining the optimal timing, both in terms of which stage of injury will neuromodulation be most effective, and in terms of timing of multiple interventions. Evidence suggests that brain and spinal cord reorganization early after injury are correlated with the amount of recovery[14], which would suggest that interventions may have greater effect in the early stages after injury. Indeed, there is some evidence to support the concept that greater effects are achieved earlier after spinal cord injury in human studies, however there is also potential for improvements even in the chronic stage many years after injury (for review see[23]). Furthermore, recent experimental work revealed the importance of sequential (rather than concurrent) timing of multiple neuromodulatory interventions. When

animals with experimental stroke[24] or SCI[25] were treated with a neuroplasticity-enhancing anti-Nogo immunotherapy combined with rehabilitation, early high-intensity training during the 2 week immunotherapy dosing period (the active axonal growth phase) led to poorer performance than each therapy alone. However, sequential therapy, which enabled active growth and then stabilisation before commencing intensive training, led to significant recovery of motor functions. This highlights the need to consider whether to apply neuromodulation interventions during a "plastic" vs stabilisation phase in future study designs. There are different views regarding the relative timing of neuromodulatory stimulation and training, as there are thought to be two classes of mechanisms that govern decisions about timing of the stimulation relative to training**.** The principles of homeostatic plasticity would dictate that inhibitory stimulation be used in advance of training, whereby the mechanism of returning excitability to pre-stimulation levels would be synergistic with the activity-related increase in excitability. Conversely, principles of gating would dictate that excitatory stimulation be used concurrently with training such that the two mechanisms would have an additive effect[11]. More work is needed on establishing the optimal timing for neuromodulation-based interventions for SCI and, again, understanding mechanisms will be of critical importance.

Clinical trial design for neuromodulation interventions for SCI

The great variability in clinical presentation of SCI is one of the major challenges in identifying stimulation-based interventions that have broad applicability. Functional movement is strongly dependent of the amount of descending corticospinal activation that reaches the spinal circuits to activate muscles response, this is true for hand function[26] as well as walking function[27]. The International Standards for Neurological Classification of Spinal Cord Injury[28] classifies SCI into "complete" (insufficient residual spinal transmission pathways to allow sensory perception or volitional movement) and "incomplete" (some degree of residual spinal transmission to allow sensory perception or volitional movement). In addition, there is evidence that some individuals who appear to have complete SCI, do in fact have some residual remaining transmission that is evident on electrophysiologic assessment, a phenomenon referred to as "discomplete" SCI[29]. Following SCI, the nervous system undergoes many changes, and these changes may progress at different rates in different individuals. Despite this potential for neurologic change, large longitudinal studies have indicated that electrophysiologic measures acquired early after SCI strongly predict motor scores and functional abilities at one-year post SCI for both upper and lower extremities[30,31]. Future studies will need to determine which interventions have the most beneficial influence on these outcomes.

The majority of clinical trials that use stimulation approaches for restoration of motor function enrol individuals who have sufficient residual spinal transmission for some degree of volitional

movement. While there are exceptions, to date those studies that have enrolled individuals with complete or discomplete injuries have shown that while it is possible to elicit movement, the technology has yet to facilitate the amount of motor activation that is required for functional hand or lower extremity activity. The differences in the requirements to achieve functional hand or lower extremity movement between persons with more severe SCI who lack volitional control and persons with residual volitional control indicates that research approaches for these two sub-populations must differ. For studies in persons with insufficient residual spinal cord transmission to produce movement, the goal is to demonstrate proof-of-concept for the potential of an intervention to influence movement that is supportive of real-world function (e.g. hand grasp, stepping, sitting balance). Conversely, for studies in individuals with residual volitional control that are intended to assess the rehabilitation value of an intervention, the intervention must be associated with a meaningful improvement in ability to perform an activity. There are valuable recommendations available to guide the development of the latter type of clinical trials from the proof-of-concept stage to clinical efficacy stage[32]. It is important to recognize that even large multicentre efficacy studies, wherein an experimental intervention is compared to a viable control condition, have criteria and restrictions that may limit direct translation to the real world of the clinic. As such these trials, at best, show efficacy rather than effectiveness. Effectiveness of any intervention can only be shown based on the value of the intervention under real-world clinical conditions. For this reason, there is growing interest in pragmatic clinical trials, wherein an experimental intervention is included as part of real-world clinical practice to evaluate its effectiveness.

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